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(54) Azithromycin monohydrate isopropanol clathrate and methods for the manufacture thereof.

(57) A novel form of azithromycin and processes for preparation of pure azithromycin monohydrate isopropanol clathrate (3 molecules of isopropanol for every 10 molecules of azithromycin monohydrate) has been obtained. Preparation of the novel form of azithromycin comprises the steps of dissolving azithromycin in isopropanol, followed by the slow addition of water to the organic solution.

EP 0 984 020 A2

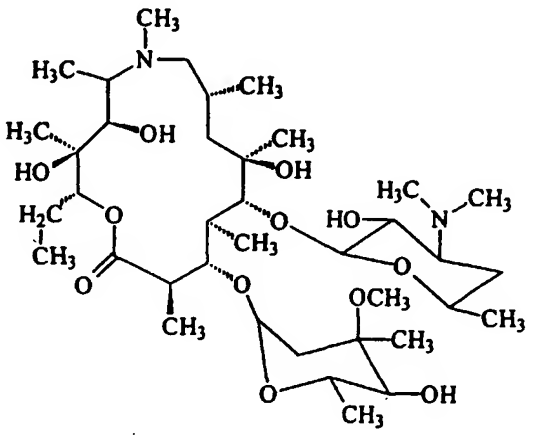
Description

FIELD OF THE INVENTION

[0001] This invention relates to a new form of azithromycin, namely azithromycin monohydrate isopropanol clathrate, which has improved properties over amorphous azithromycin, azithromycin monohydrate and azithromycin dihydrate. This invention also relates processes for the manufacture of azithromycin monohydrate isopropanol clathrate.

BACKGROUND OF THE INVENTION

[0002] Azithromycin, 9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, is a semi-synthetic macrolide antibiotic which can be classified as a member of the second-generation erythromycin antibacterial agent. Azithromycin has the following structure (I):



(I)

[0003] The spectrum of azithromycin's antibacterial activity has been reported by Aronoff, *et al (J. Antimicrob. Chemother.*, **1987**, 19, 275). Its mode of action has been reviewed by Retsema, *et al (Antimicrob. Ag. Chemother.*, **1987**, *31*, 1939)n, and its pharmacology has been reviewed by a number of investigators *(J. Antimicrob. Chemother.*, **1993**, *31*, Suppl. E, 1-198).

[0004] Three forms of Azithromycin are known. Anhydrous azithromycin is reported as an amorphous crude product (foam) in Canadian Patent 1 191 843 (example 1). It is obtained by evaporating the final solvent (e.g. chloroform) used in the process of preparation of azithromycin. It is not a crystalline product and therefore can not be made in pure form *per se* in commercial scale. In laboratory scale, it can be obtained in pure form by chromatography of the crude final product or by dissolving pure crystalline azithromycin mono- or dihydrate in an organic solvent and evaporating the said solvent to obtain amorphous anhydrous azithromycin.

[0005] Canadian patents 1,202,620, 1,202,619, 1, 202,963 and 1,314,876 teach the process of making azithromycin monohydrate but do not claim the resulting product. Furthermore, these patents do not provide a description of the drying process (temperature or pressure). Canadian patents 1,191,843 and 1,202,963 claim azithromycin monohydrate as a new form of azithromycin. The theoretical percentage of water in azithromycin monohydrate is 2.3%. However, Canadian Patent 1,314,876 reports a value of 3.92%, and a value of 3.2% is reported in Canadian patent 1,314,876. No reference to the percentage of water is made in the other above-mentioned Canadian patents. Azithromycin monohydrate is known to be hygroscopic (see for example European Patent 298 650 B1). This is an undesirable property since it complicates formulation of azithromycin drug product and can adversely effect its stability on long term storage.

[0006] Canadian patent 1,314,876 claims azithromycin dihydrate and, in contrast to azithromycin monohydrate, a full description of the drying process used for obtaining the product is provided. Low boiling solvents (tetrahydrofuran and hexane) are used with 3-4 equivalent moles of water to obtain the crystalline product, which is dried under vacuum at low temperatures (20-40 °C). The use of low boiling solvents for crystallisation and low temperatures for vacuum drying of the product are prescribed presumably to control the desirable amount of water that must be evaporated to afford azithromycin dihydrate. Excess loss of water, caused by higher temperature vacuum drying, could result in the formation of azithromycin monohydrate. In contrast to anhydrous azithromycin and azithromycin monohydrate, azithromycin dihydrate has desirable properties for formulation. It is crystalline and can therefore be obtained in pure form

in commercial scale. It is not hygroscopic and therefore does not pose a problem during formulation or adversely effect the stability of the resulting drug product.

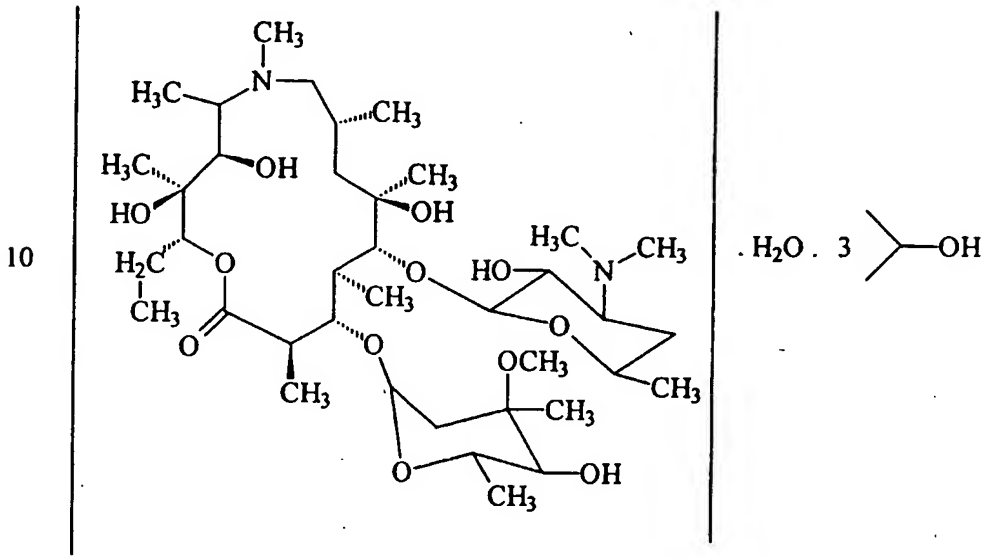
[0007] It is clear that anhydrous and monohydrate forms of azithromycin are not suitable for formulation. The processes referred to in Canadian Patent 1 314 876 for the preparation of azithromycin dihydrate, while producing a non-hygroscopic form of azithromycin, have a number of disadvantages:

1. Water immiscibility of the organic solvent mixture (tetrahydrofuran plus hexane) can cause problems in obtaining pure material since crystallisation processes are known to afford pure material when the antisolvent is miscible with the solvent used to dissolve the crude product.

2. The drying process must be very carefully controlled since an increase in temperature will cause the transformation of the non-hygroscopic dihydrate to the hygroscopic monohydrate.

3. The use of low boiling point solvents is complicated by their toxicity and possibility of formation of explosive peroxide during solvent recovery.

[0008] It has now been surprisingly found that slow addition of water to an isopropanol solution of azithromycin results in the formation of a new form of azithromycin, namely azithromycin monohydrate isopropanol clathrate of formula II:



II

[0009] The physical properties of this product and the processes used for its preparation have a number of major advantages over the existing azithromycin product forms and the procedures used for their preparation.

[0010] First, azithromycin monohydrate isopropanol clathrate is crystalline and, in contrast to anhydrous azithromycin, may be obtained in pure form.

[0011] Second, azithromycin monohydrate isopropanol clathrate is not hygroscopic and, in contrast to anhydrous azithromycin and azithromycin monohydrate, may be used in formulations of the drug product as tablets or capsules with excellent stability profiles.

[0012] Third, azithromycin monohydrate isopropanol clathrate is, in contrast to azithromycin dihydrate, obtained conveniently and reproducibly by crystallisation from isopropanol water.

[0013] Fourth, in contrast to azithromycin dihydrate, azithromycin monohydrate isopropanol clathrate is obtained by crystallisation from inexpensive solvents.

[0014] Fifth, in contrast to azithromycin dihydrate, azithromycin monohydrate isopropanol clathrate is prepared from environmentally safe solvents (hexane: Class 2; isopropanol and tetrahydrofuran: Class 3, see Federal Register, Vol. 62, No. 247,67381, Dec 24, 1997).

[0015] Sixth, the experimental conditions are simple and applicable to large-scale production.

7. The process of claim 2 wherein vacuum drying is carried out at a temperature of 50°C to 60°C.

8. The process of claim 2 or 7 wherein the vacuum drying is carried out under 6 to 10 mm Hg.

9. A process for the preparation of azithromycin monohydrate isopropanol clathrate characterised by the following x-ray powder diffraction pattern expressed in terms of "D" spacings and Relative Intensity:

Angle (°2θ)	D-value (A)	Relative Intensity %
4.985	17.712	0.2
5.605	15.754	0.3
6.205	14.232	1.3
7.350	12.017	1.7
7.855	11.246	7.5
8.240	10.721	0.4
8.830	10.006	0.3
9.400	9.401	4.1
9.790	9.027	100.0
10.245	8.627	0.4
11.165	7.918	8.8
11.365	7.779	2.5
11.935	7.409	1.4
12.495	7.078	4.3
13.955	6.341	2.2
14.250	6.210	1.2
14.645	6.044	2.6
14.810	5.977	1.8
15.270	5.798	5.3
15.700	5.640	2.9
15.990	5.538	0.9
16.595	5.338	1.1
17.040	5.199	2.1
17.450	5.078	1.5
18.035	4.915	0.5
18.375	4.824	1.0
18.540	4.782	1.0
19.060	4.653	2.8
19.670	4.510	2.8
19.995	4.437	1.7
20.425	4.345	2.7
20.885	4.250	1.1
21.030	4.221	0.8
21.740	4.085	0.8
22.540	3.941	0.8
23.470	3.787	0.5
24.125	3.686	0.6
24.475	3.634	0.7
24.705	3.601	0.7
25.245	3.525	0.6
25.510	3.489	0.9
26.145	3.406	0.8
26.510	3.360	0.2
28.320	3.145	0.3

(continued)

X-RAY DIFFRACTION			
Angle °2θ	D-value(Å)	Relative Intensity %	
14.250	6.210	1.2	
14.645	6.044	2.6	
14.810	5.977	1.8	
15.270	5.798	5.3	
15.700	5.640	2.9	
15.990	5.538	0.9	
16.595	5.338	1.1	
17.040	5.199	2.1	
17.450	5.078	1.5	
18.035	4.915	0.5	
18.375	4.824	1.0	
18.540	4.782	1.0	
19.060	4.653	2.8	
19.670	4.510	2.8	
19.995	4.437	1.7	
20.425	4.345	2.7	
20.885	4.250	1.1	
21.030	4.221	0.8	
21.740	4.085	0.8	
22.540	3.941	0.8	
23.470	3.787	0.5	
24.125	3.686	0.6	
24.475	3.634	0.7	
24.705	3.601	0.7	
25.245	3.525	0.6	
25.510	3.489	0.9	
26.145	3.406	0.8	
26.510	3.360	0.2	
28.320	3.145	0.3	
29.200	3.056	0.3	
29.410	3.035	0.3	
29.825	2.993	0.2	
30.170	2.960	0.2	
32.750	2.732	0.4	
33.565	2.668	0.4	
34.640	2.587	0.2	
35.295	2.541	0.3	
36.135	2.484	0.3	
37.490	2.397	0.2	
39.710	2.268	0.2	

[0036] The invention will be more fully understood by the following examples, which illustrate the present invention, but are not to be considered limiting to the scope of the invention.

EXAMPLE 1

[0037] Anhydrous azithromycin (1 kg) is dissolved in isopropanol (2.8 kg) by warming. The solution is stirred vigorously and water (4.35 kg) is added slowly over a 1-hour period. The mixture is cooled to 20 °C and stirred for an additional 6 hours at this temperature. The resulting product is filtered and washed with a 40:60 mixture of isopropanol-

water. The cake was then dried vacuum (6 to 10 mm Hg) at 50 °C for 12 hours. Yield 0.88 kg (88%).

EXAMPLE 2

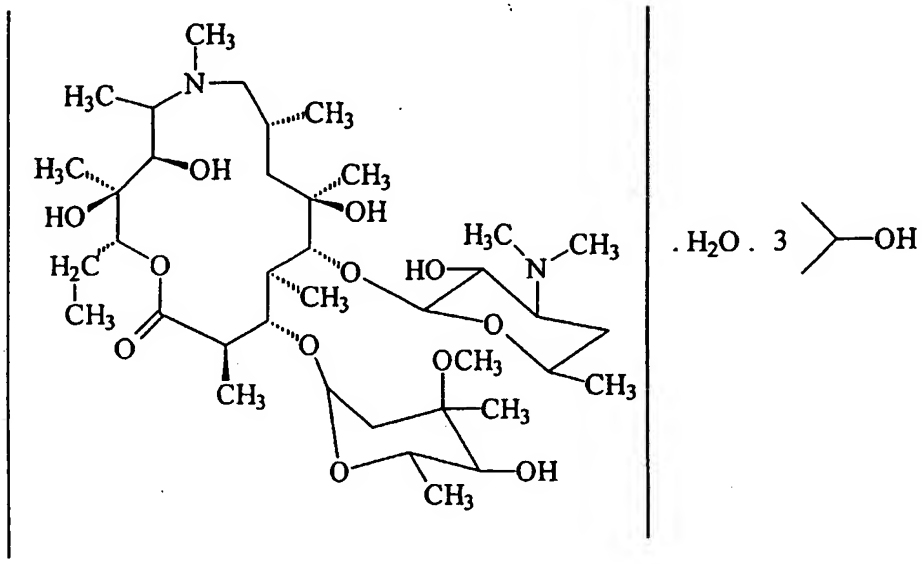
[0038] Azithromycin monohydrate (1 kg) is dissolved in isopropanol (2.8 kg) by warming. The solution is stirred vigorously and water (4.35 kg) is added slowly over a 1-hour period. The mixture is cooled to 20 °C and stirred for an additional 6 hours at this temperature. The resulting product is filtered and washed with a 40:60 mixture of isopropanol-water. The cake was then dried vacuum (6 to 10 mm Hg) at 50 °C for 12 hours. Yield 0.88 kg (88%).

EXAMPLE 3

[0039] Azithromycin dihydrate (1 kg) is dissolved in isopropanol (2.8 kg) by warming. The solution is stirred vigorously and water (4.35 kg) is added slowly over a 1-hour period. The mixture is cooled to 20 °C and stirred for an additional 6 hours at this temperature. The resulting product is filtered and washed with a 40:60 mixture of isopropanol-water. The cake was then dried vacuum (6 to 10 mm Hg) at 50 °C for 12 hours. Yield 0.88 kg (88%).

Claims

1. A compound of formula II:



2. A process for the preparation of azithromycin monohydrate isopropanol clathrate which comprises the steps of:

   (a) Dissolving azithromycin in isopropanol and slowly adding water to the resulting solution;
   (b) Filtering and washing the product with a mixture of isopropanol water;
   (c) Vacuum drying the product.

3. The process of claim 2 wherein the dissolution of crystalline azithromycin is carried out in a volume of solvent only sufficient to dissolve the azithromycin.

4. The process of claim 2 wherein water is added over a period of one hour.

5. The process of claim 2 or 4 wherein the addition of water to the resulting solution is carried out between 0°C to 30°C.

6. The process of claim 5 wherein the addition of water is carried between 15°C to 25°C.

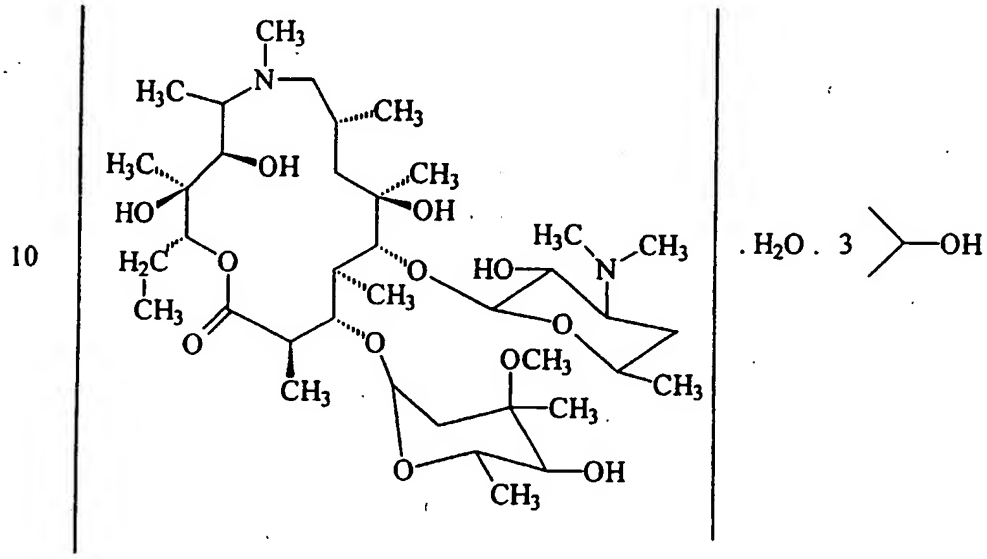
[0016] Seventh, the present processes are reproducible in a wide spectrum of physical conditions and consistently afford azithromycin monohydrate isopropanol clathrate with a constant ratio of azithromycin, water and isopropanol (vacuum drying at 1 - 10 mm Hg at 50° to 60 °C for 12 to 24 hours).

[0017] Eighth, the product generated by the processes of the present invention is highly pure.

[0018] Ninth, the processes taught in this invention afford high yields of the product within the range of 88% to 93% (first crop). The remainder of the product is conveniently recovered from the mother liquor by evaporation of isopropanol under reduced pressure.

BRIEF DESCRIPTION OF THE INVENTION

[0019] In one aspect, the invention relates to a compound of formula II:



[0020] In another aspect, the invention relates to a process for the preparation of azithromycin monohydrate isopropanol clathrate which comprises the steps of:

(a) Dissolving azithromycin in isopropanol and slowly adding water to the resulting solution;

(b) Filtering and washing the product with a mixture of isopropanol water;

(c) Vacuum drying the product.

BRIEF SUMMARY OF THE DRAWINGS

[0021] Figure 1 is a powder X-Ray diffraction of anhydrous azithromycin.

[0022] Figure 2 is a powder X-Ray diffraction of azithromycin monohydrate.

[0023] Figure 3 is a powder X-Ray diffraction of azithromycin monohydrate isopropanol clathrate.

[0024] Figure 4 is a powder X-Ray diffraction of azithromycin dihydrate.

[0025] Figure 5 is a DSC of azithromycin monohydrate.

[0026] Figure 6 is a DSC of azithromycin monohydrate isopropanol clathrate.

[0027] Figure 7 is an IR spectrum of azithromycin monohydrate and azithromycin monohydrate isopropanol clathrate.

DETAILED DESCRIPTION OF THE INVENTION

[0028] The present invention describes a new form of azithromycin monohydrate, namely azithromycin monohydrate isopropanol clathrate and the processes for the preparation of pure azithromycin monohydrate isopropanol clathrate.

[0029] Previously known forms of azithromycin (anhydrous, monohydrate, and dihydrate) may serve as the starting material in the present, all of which are commercially available.

[0030] According to this invention, azithromycin monohydrate isopropanol clathrate contains three molecules of isopropanol for every ten molecules of azithromycin monohydrate.

[0031] The process comprises the dissolution of azithromycin in isopropanol to which water is added slowly while stirring, resulting in the precipitation of crystalline azithromycin monohydrate isopropanol clathrate. The volume of solvent used is such as to be sufficient to dissolve azithromycin. The addition of the water is carried out between 0° and 30°C and preferably between 15°C to 25°C. The product is filtered and washed with a mixture of water-isopropanol and dried under vacuum (1-10 mm Hg) at 50°C to 60°C for 12-24 hours to obtain azithromycin monohydrate isopropanol clathrate in high yields. Extension of vacuum drying does not reduce either the water content or the isopropanol content of azithromycin monohydrate isopropanol clathrate.

[0032] Elemental analysis, 1HNMR, 13C NMR, and IR spectroscopy, mass spectrometry, and powder x-ray diffraction and IR have identified the azithromycin monohydrate isopropanol clathrate produced according to the invention. Figures 1 to 4 show the differences between powder x- ray diffraction of anhydrous azithromycin, azithromycin monohydrate, azithromycin monohydrate isopropanol clathrate, and azithromycin dihydrate. Comparison of Figure 3 with Figures 1,2 and 4 clearly shows the differences in the morphology of azithromycin monohydrate isopropanol clathrate with anhydrous azithromycin, azithromycin monohydrate and azithromycin dihydrate. These figures also indicate that azithromycin monohydrate isopropanol clathrate is free of azithromycin dihydrate.

[0033] Differential Scanning Colorimetry (DSC) of azithromycin monohydrate (157.99 °C) and azithromycin monohydrate isopropanol clathrate (149.88 °C) are shown in Figures 5 and 6.

[0034] Near IR spectra of azithromycin monohydrate and azithromycin monohydrate isopropanol clathrate are shown in Figure 7. The major difference is at 6800 cm^{-1} at which the clathrate shows a medium absorption.

[0035] The water content of azithromycin monohydrate isopropanol clathrate was measured by the Karl-Fischer method and its isopropanol content was determined by gas chromatography.

X-RAY DIFFRACTION			
Instrumental Parameters			
Instrument: Philips PW3710 Based Diffractometer with APD Software Ver. 3.6			
Sample preparation	unground	Holder type:	Philips Standard
Radiation:	$CuK\alpha_1$, (λ = 1.54056 Å)	Operation	40KV X 40mA
		Power:	
Scanning Mode:	Step	Divergence Slit:	0.5°
Scanning Range (°2θ):	4.0 - 40.0	Receiving Slit:	0.2mm
Step Size (°2θ):	0.020	Scattering Slit:	0.50
Measuring Time (sec/step):	1.20		
Angle °2θ	D-value(Å)	Relative Intensity %	
4.985	17.712	0.2	
5.605	15.754	0.3	
6.205	14.232	1.3	
7.350	12.017	1.7	
7.855	11.246	7.5	
8.240	10.721	0.4	
8.830	10.006	0.3	
9.400	9.401	4.1	
9.790	9.027	100.0	
10.245	8.627	0.4	
11.165	7.918	8.8	
11.365	7.779	2.5	
11.935	7.409	1.4	
12.495	7.078	4.3	
13.955	6.341	2.2	

(continued)

Angle (°2θ)	D-value (A)	Relative Intensity %
29.200	3.056	0.3
29.410	3.035	0.3
29.825	2.993	0.2
30.170	2.960	0.2
32.750	2.732	0.4
33.565	2.668	0.4
34.640	2.587	0.2
35.295	2.541	0.3
36.135	2.484	0.3
37.490	2.397	0.2
39.710	2.268	0.2

which comprises the steps of:

(a) Dissolving azithromycin in isopropanol and slowly adding water to the resulting solution;
(b) Filtering and washing the product with a mixture of isopropanol water;
(c) Vacuum drying the product.

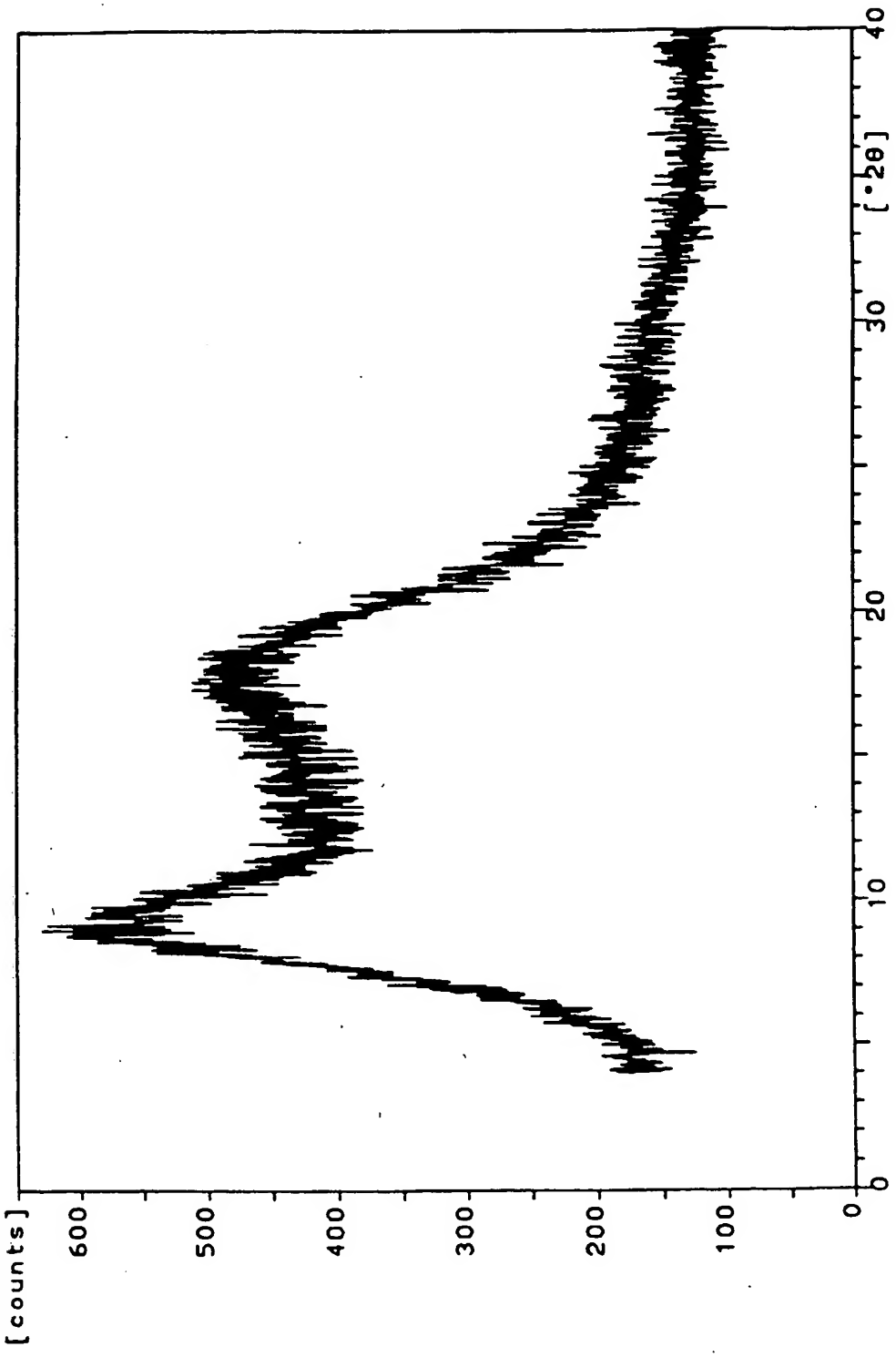


Figure 1

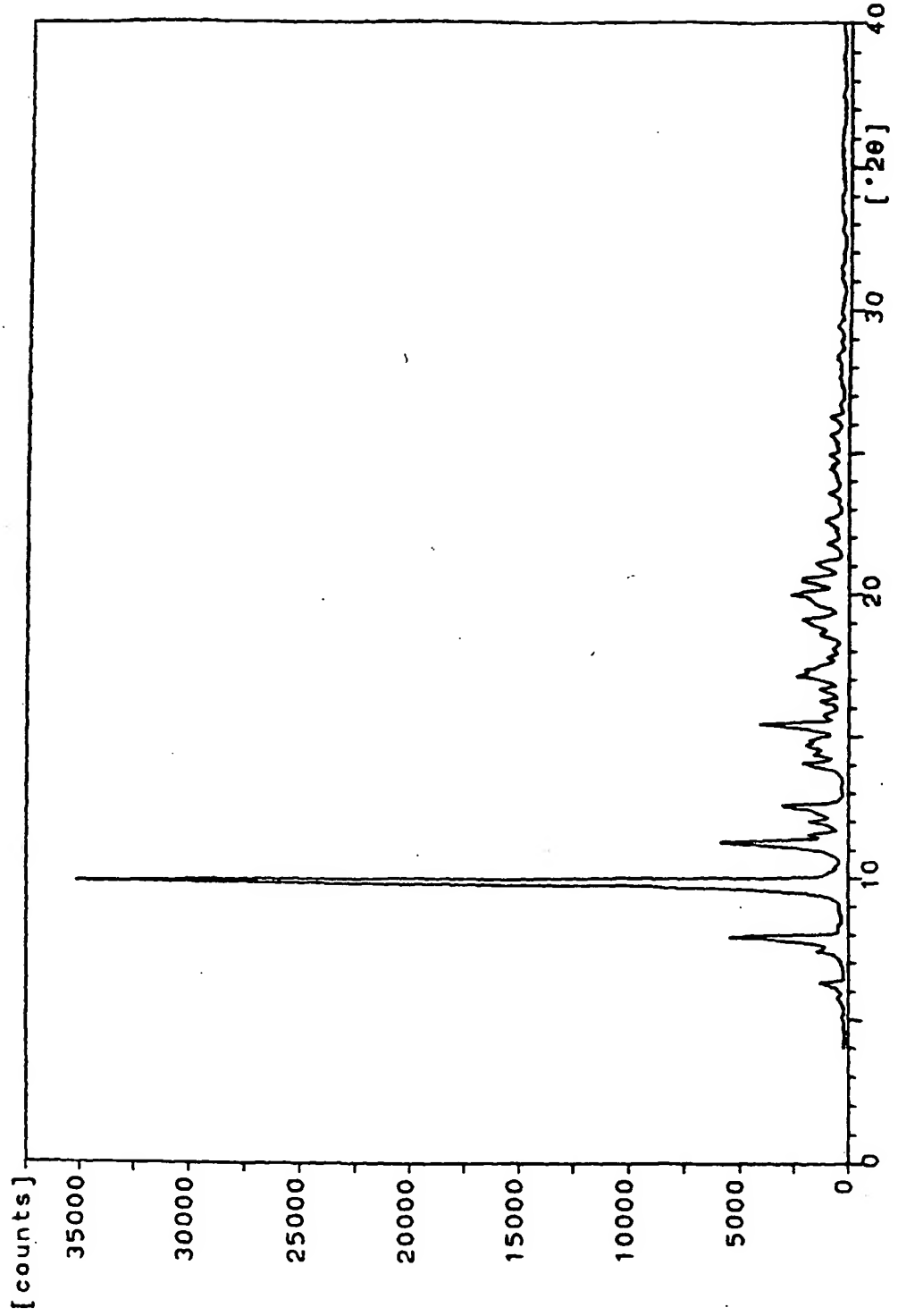

[counts]
35000
30000
25000
20000
15000
10000
5000
0
0
10
20
30
40
[°2θ]

Figure 2

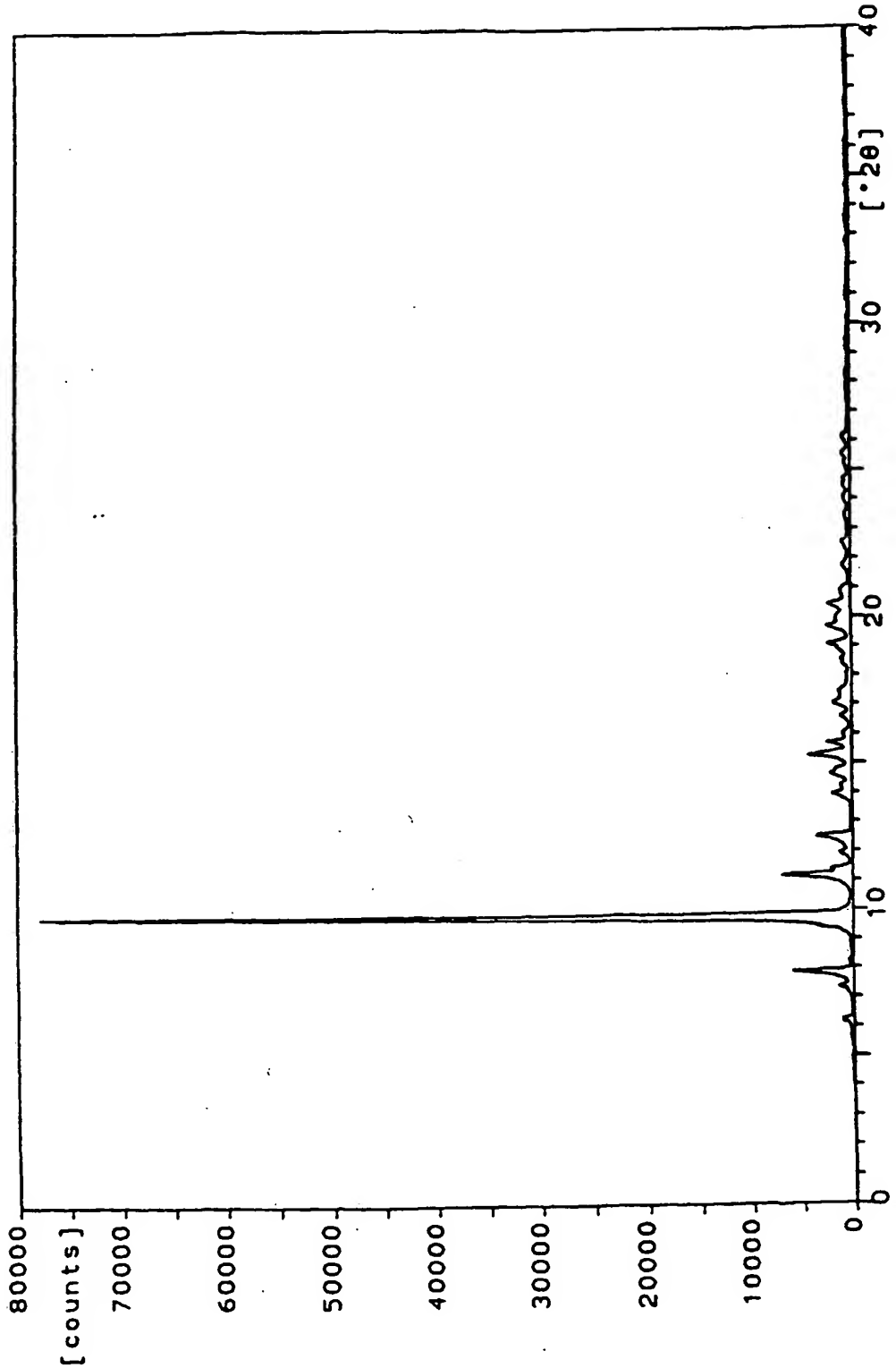

80000
[counts]
70000
60000
50000
40000
30000
20000
10000
0
0
10
20
30
40
[°2θ]

Figure 3

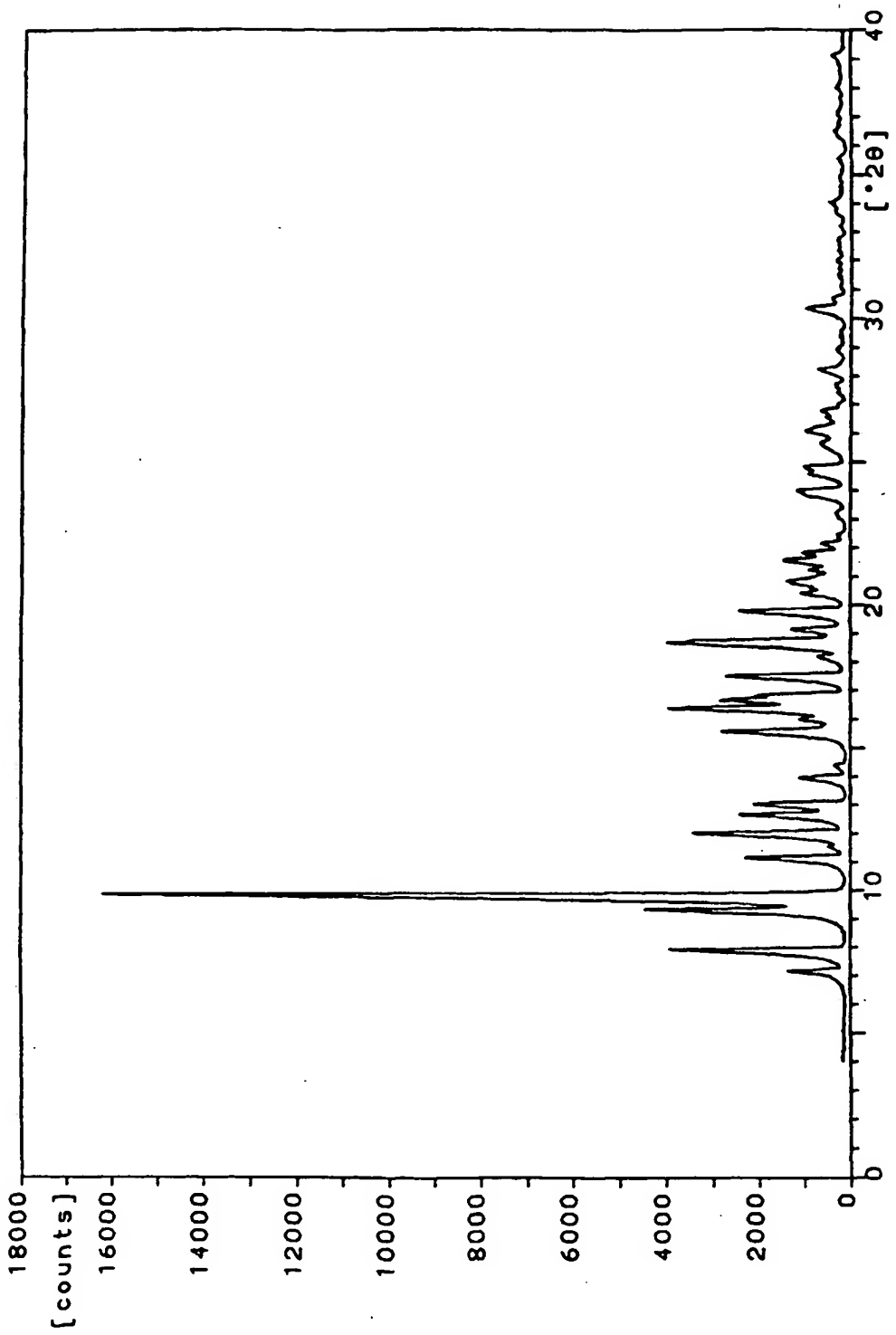

[counts]
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
0
10
20
30
40
[°2θ]

Figure 4

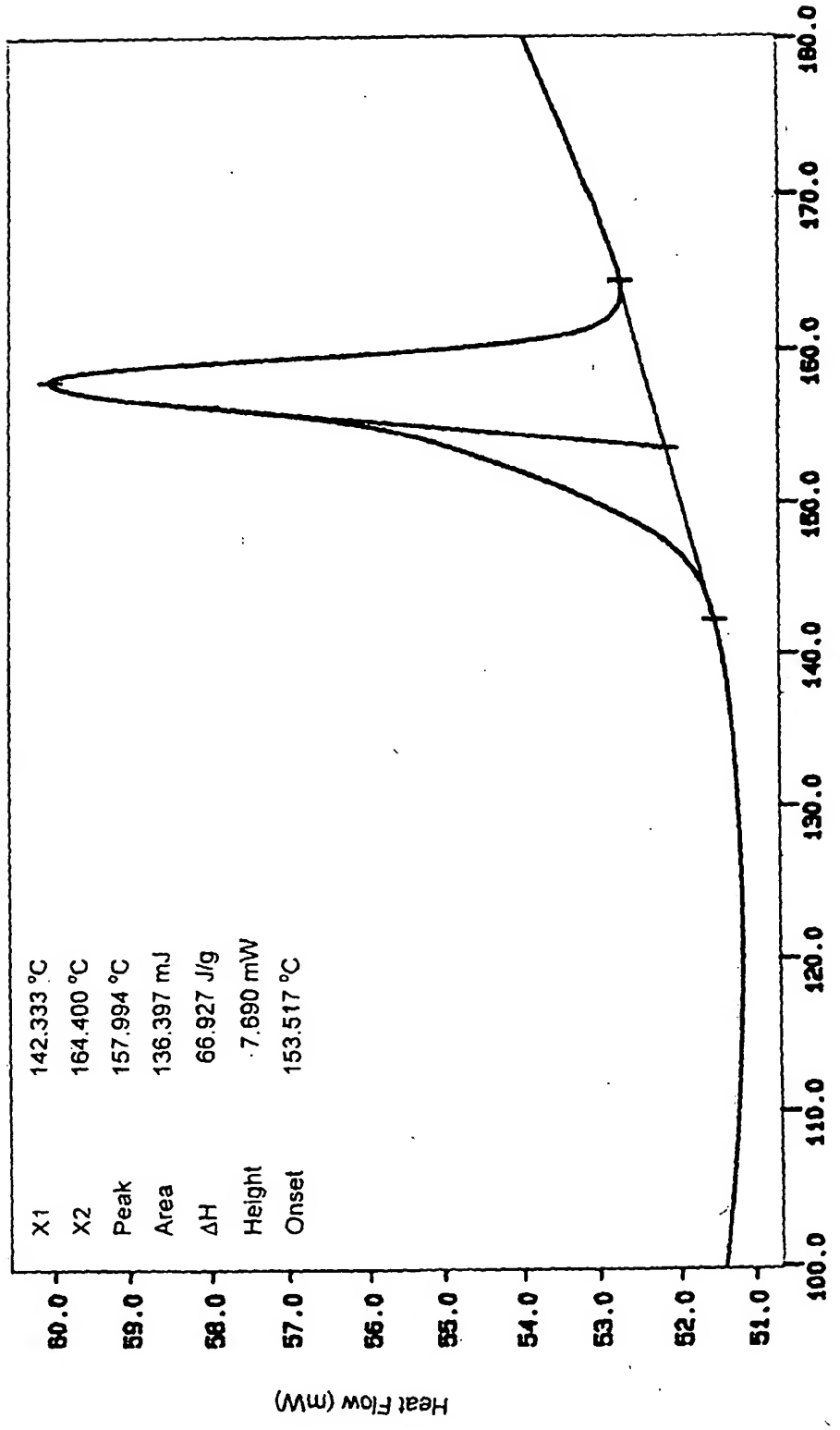

X1 142.333 °C
X2 164.400 °C
Peak 157.994 °C
Area 136.397 mJ
ΔH 66.927 J/g
Height 7.690 mW
Onset 153.517 °C
60.0
59.0
58.0
57.0
56.0
55.0
54.0
53.0
52.0
51.0
Heat Flow (mW)
100.0
110.0
120.0
130.0
140.0
150.0
160.0
170.0
180.0

Figure 5

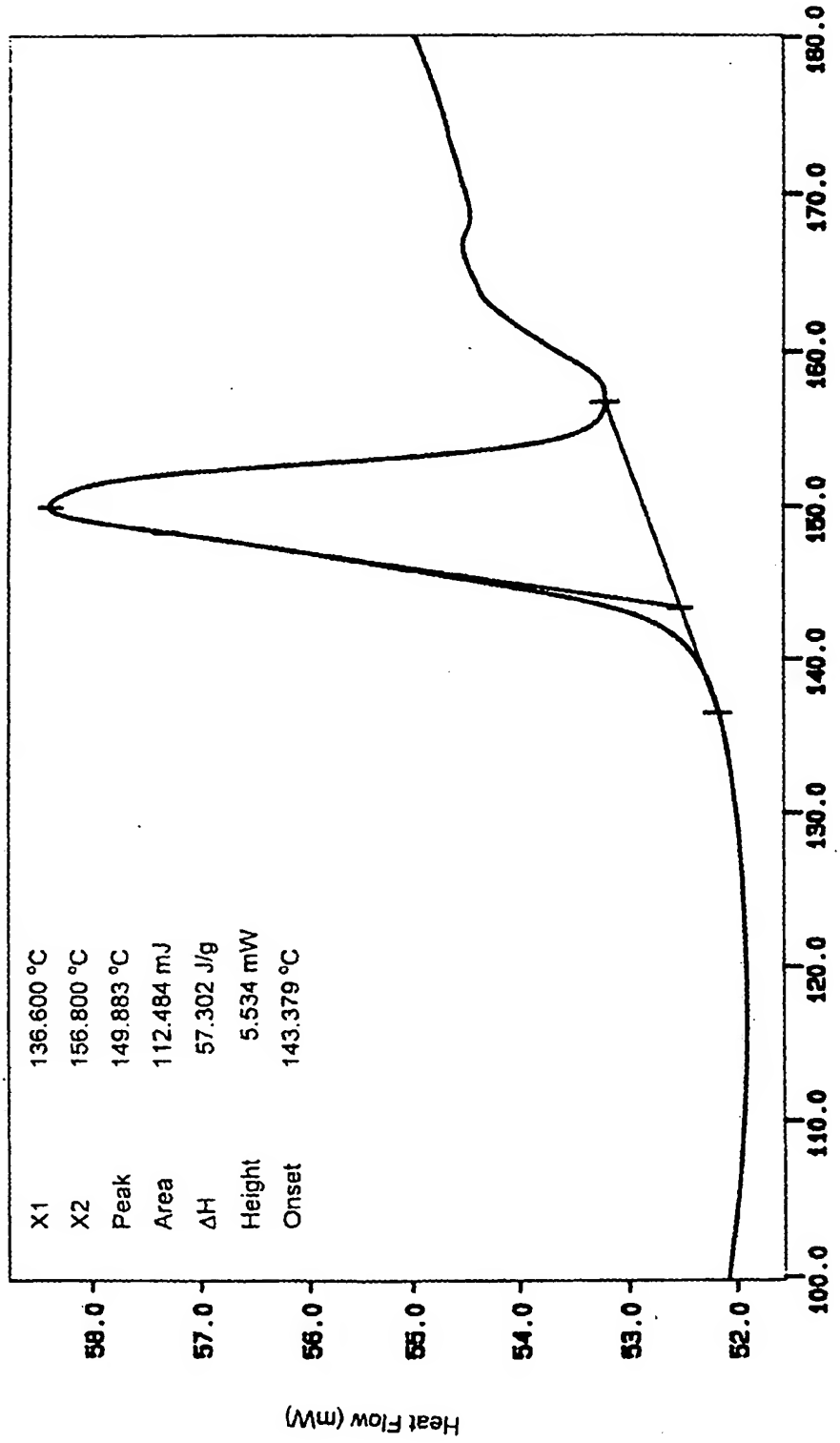

X1 136.600 °C
X2 156.800 °C
Peak 149.883 °C
Area 112.484 mJ
ΔH 57.302 J/g
Height 5.534 mW
Onset 143.379 °C
58.0
57.0
56.0
55.0
54.0
53.0
52.0
Heat Flow (mW)
100.0
110.0
120.0
130.0
140.0
150.0
160.0
170.0
180.0

Figure 6

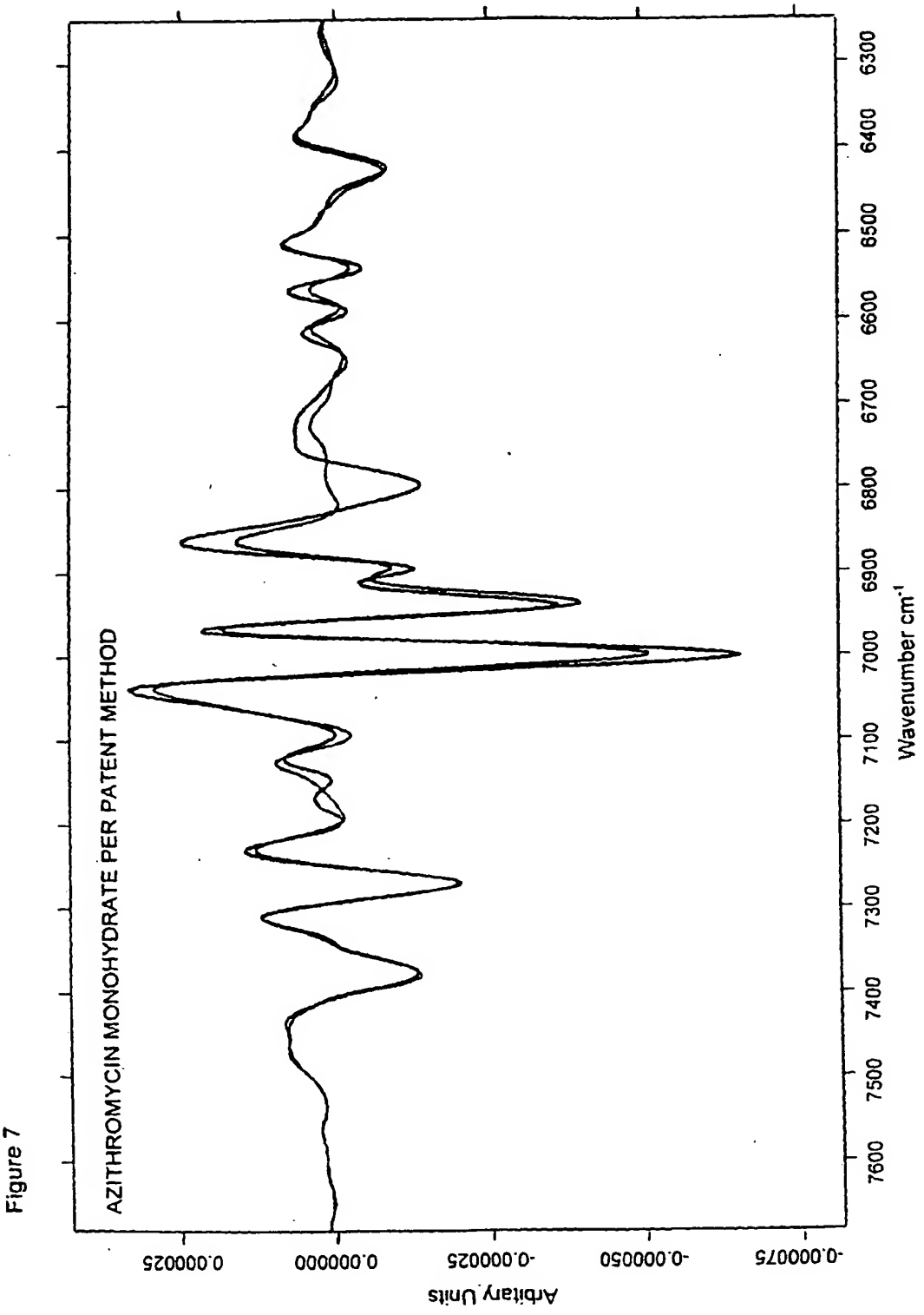

AZITHROMYCIN MONOHYDRATE PER PATENT METHOD
Arbitary Units
0.000025
0.000000
-0.000025
-0.000050
-0.000075
Wavenumber cm-1
7600
7500
7400
7300
7200
7100
7000
6900
6800
6700
6600
6500
6400
6300

Figure 7

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Office européen des brevets

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(54) Azithromycin monohydrate isopropanol clathrate and methods for the manufacture thereof.

(57) A novel form of azithromycin and processes for preparation of pure azithromycin monohydrate isopropanol clathrate (3 molecules of isopropanol for every 10 molecules of azithromycin monohydrate) has been obtained. Preparation of the novel form of azithromycin comprises the steps of dissolving azithromycin in isopropanol, followed by the slow addition of water to the organic solution.

EP 0 984 020 A3

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 99 30 6612

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
A	EP 0 298 650 A (PFIZER) 11 January 1989 (1989-01-11) * page 4, preparation 1 *	1,2	C07H17/08
A	WO 97 38000 A (ABBOTT LAB) 16 October 1997 (1997-10-16) * the whole document *	1,2	
P,A	WO 99 02541 A (BIOCHEMIE SA ;DIAGO JOSE (ES); BOSCH IMMACULADA (ES); CENTELLAS VI) 21 January 1999 (1999-01-21) * claims 1-13; example 3 *	1,2	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

C07H

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	15 August 2000	Scott, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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P : intermediate document

T : theory or principle underlying the invention
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D : document cited in the application
L : document cited for other reasons

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EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 30 6612

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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15-08-2000

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0298650 A	11-01-1989	WO 8900576 A	26-01-1989
		AP 44 A	27-07-1989
		AT 72446 T	15-02-1992
		AU 604553 B	20-12-1990
		AU 1883988 A	12-01-1989
		BA 98213 B	02-08-1999
		BG 47348 A	15-06-1990
		CA 1314876 A	23-03-1993
		CN 1030422 A,B	18-01-1989
		CS 8804896 A	14-03-1990
		CY 1776 A	20-10-1995
		DD 271705 A	13-09-1989
		DE 3868296 A	19-03-1992
		DK 380688 A	10-01-1989
		FI 900087 A,B,	08-01-1990
		GR 3003737 T	16-03-1993
		HK 127594 A	25-11-1994
		HU 9500738 A	28-11-1995
		IE 60354 B	29-06-1994
		IL 86979 A	15-11-1992
		IN 168879 A	29-06-1991
		JP 1038096 A	08-02-1989
		JP 1903527 C	08-02-1995
		JP 6031300 B	27-04-1994
		KR 9006218 B	25-08-1990
		LV 10624 A	20-04-1995
		MX 12213 A	01-05-1993
		NZ 225338 A	26-02-1990
		OA 8743 A	31-03-1989
		PT 87933 A,B	30-06-1989
		RO 107257 A	30-10-1993
		SG 27794 G	14-10-1994
		SI 8811325 A	31-12-1996
		RU 2066324 C	10-09-1996
		YU 132588 A	28-02-1990
		ZA 8804925 A	28-02-1990
WO 9738000 A	16-10-1997	US 5808017 A	15-09-1998
		CA 2250941 A	16-10-1997
		EP 0970099 A	12-01-2000
WO 9902541 A	21-01-1999	AU 8973398 A	08-02-1999
		EP 0994889 A	26-04-2000

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82